POTENTIATION OF IMMUNE RESPONSES WITH LIPOSOMAL ADJUVANTS

This application is a continuation-in-part of Ser. No. 07/425,727, filed Oct. 23, 1989, now U.S. Pat. No. 5,231,112, which is a continuation-in-part of Ser. No. 06/773,429, filed Sep. 10, 1985, now U.S. Pat. No. 4,891,208, which is a continuation-in-part of Ser. No. 06/721,630, filed Apr. 10, 1985, now U.S. Pat. No. 4,721,612, which is a continuation-in-part of Ser. No. 06/599,691, filed Apr. 12, 1984, now abandoned. This application is also a continuation-in-part of Ser. No. 07/397,777, filed Aug. 23, 1989, now abandoned, which is a continuation-in-part Ser. No. 07/277,854, filed Nov. 30, 1988, now abandoned, and is a continuation-in-part of Ser. No. 07/236,701, filed Aug. 25, 1988, now abandoned, and is a continuation-in-part of Ser. No. 07/236,702, filed Aug. 25, 1988, now abandoned. This application is also a continuation-in-part of Ser. No. 07/277,854, filed Nov. 30, 1988, now abandoned, which is a continuation-in-part of Ser. No. 07/128,974, filed Dec. 4, 1987, now abandoned, and is a continuation-in-part of Ser. No. 07/061,186, filed Jun. 11, 1987, now abandoned, which is a continuation-in-part of Ser. No. 06/934,151, filed Nov. 24, 1986, now abandoned, and is a continuation-in-part of Ser. No. 06/873,584, filed Jun. 12, 1986, now abandoned. This application is also a continuation-in-part of Ser. No. 07/236,701, filed Aug. 25, 1988, now abandoned, which is a continuation-part of Ser. No. 07/128,974, filed Dec. 4, 1987, now abandoned, and is a continuation-in-part of Ser. No. 07/236,702, filed Aug. 25, 1988, now abandoned.

FIELD OF THE INVENTION

This invention relates to a number of liposomal dosage forms for therapeutic delivery of bioactive agents and for use in the vaccine arts.

In a first aspect, the present invention relates to a high integrity liposome comprising at least one stabile lipid and at least one peptide-like therapeutic agent (including an antigen or immunogen) associated with said liposome, adapted for parenteral administration to an animal, including a human. Also disclosed is a method of manufacture and use. Such liposomes are particularly useful for extended elaboration of peptide therapeutic agents as well as serving to protect said agents from degradation in the physiological environment. High integrity liposomes according to the present invention maintain their activity at the site of topical or parenteral administration, for example, after intramuscular, intraperitoneal, intraocular, intramammary or subcutaneous administration for periods often in excess of 24 hours. Therapeutic methods are also disclosed which utilize the extended elaboration of the liposomal dosage forms of the present invention to provide a treatment regimen which may be used to treat numerous conditions with a less invasive methodology than intravenous, intra-arterial or even daily injection.

Immunogenic dosage forms are also presented. These innumogenic dosage forms of the present invention exhibit surprising immunogenic activity.

In a second aspect of the present invention, certain stabile liposomes, e.g., DMPC/cholesterol liposomes are disclosed for use in the vaccine arts with a dosage form particularly adapted to producing an immune response, comprising DPMC/cholesterol liposomes, optionally in an aluminum hydroxide gel, and an immunogen wherein said DPMC/cholesterol liposomes and immunogen are present in an immunization dose, and method of use. Methods of using these dosage forms are also disclosed by the present invention.

In a third aspect of the present invention, an immunogenic dosage form is disclosed comprising a salt form of an organic acid derivative of a sterol and an immunogen wherein said organic acid derivative of a sterol and immunogen are present in an immunization dose. Also disclosed is a method of use related to these dosage forms. Methods of using these dosage forms are also disclosed.

BACKGROUND OF THE INVENTION

Peptide therapeutic agents are well known and are of increasing use in the pharmaceutical arts. Hormones, immunomodulators, and a host of newly discovered peptide and peptide-like compounds including certain immunogens are presently being administered to animals, including humans, in therapeutic regimens.

Consistent drawbacks to the parenteral administration of such peptide compounds have been the rapidity of breakdown or denaturation (loss of "native state configuration") of such compounds in the physiological environment and the difficulty of obtaining therapeutically effective dosage levels of such agents for extended periods. Infusion pumps, as well as wax or oil implants, have been employed in the therapeutic arts for chronic administration of therapeutic agents in an effort to both prolong the presence of peptide-like therapeutic agents and preserve the integrity of such agents. Furthermore, in particular cases in which the peptide-like therapeutic agent (which will be understood to include a protein or haptene) is to function as an immunogen, the peptide-like agent should (with particular reference to each epitope of the peptide-like agent) ideally maintain native state configuration for an extended period of time and additionally be presented in a fashion suitable for triggering an immunogenic response in the challenged animal.

One adaptation of the administration of peptide-like therapeutic agents is in the vaccine art. In this art immunogens are introduced into an organism in a manner so as to stimulate an immune response in the host organism. The induction of an immune response depends on many factors among which are believed to be the chemical composition and configuration of the immunogen, the immunogenic constitution of the challenged organism, and the manner and period of administration of the immunogen. An immune response has many facets, some of which are exhibited by the cells of the immune system, (e.g.,B-lymphocytes, T-lymphocytes, macrophages, and plasma cells). Immune system cells may participate in the immune response through interaction with immunogen or other cells of the immune system, the release of cytokines and reactivity to those cytokines. Immune response is conveniently (but arbitrarily) divided into two main categories—humoral and cell-mediated. The humoral component of the immune response includes production of immunoglobulins specific for the immunogen. The cell-mediated component includes the generation of delayed-type hypersensitivity and cytotoxic effector cells against the immunogen.

In some instances the immune response is the result of an initial or priming dose of an immunogen that is followed by one or more booster exposures to the immunogen. Priming with relatively strong immunogens and liposomes is discussed in "Liposomal Enhancement of the Immunogenicity of Adenovirus Type 5 Hexon and Fiber Vaccines", Kramp, W. J. et al., Infection and Immunity, 25:771–773 (1979) and "Liposomes as Adjuvants with Immunopurified Tetanus Toxoid: the Immune Response", Davis, D. et al., Immunology Letters, 14:341–8 (1986/1987).

Ideally, an immunogen will exhibit two properties; the capacity to stimulate the formation of the corresponding